APPENDIX F

Copies of information from the following web cites:

http://home.attbi.com/~bkrentzman/misc/how.things.work/dna.transcription/cytokines.html

http://www.copewithcytokines.de/cope.cgi?001668

http://www.psoriasis.org/enbrel.approval.jan02.htm

http://www.jnj.com/news_finance/402.htm

http://www.jnj.com/news/jnj news/20020329 0810.htm

News & Notices

New treatment approved for psoriatic arthritis

The U.S. Food and Drug Administration (FDA) has approved the drug etanercept (brand name Enbrel) for the treatment of psoriatic arthritis. Physicians can prescribe Enbrel by itself or in combination with methotrexate, another systemic treatment for the disease.

While other therapies are used to treat psoriatic arthritis, Enbrel is the first to receive specific FDA approval for "reducing the signs and symptoms" of active psoriatic arthritis. Psoriatic arthritis affects approximately 23 percent of people with psoriasis.

For more information about psoriatic arthritis and its treatments, request the NPF's free educational booklet *Psoriatic Arthritis*. We publish more than 30 free educational publications.

Also, the NPF recently conducted a nationwide survey to gather critical information about people who have psoriasis and psoriatic arthritis, the effect the diseases have on their lives and their experiences with treatment. Read this press release for more details.

Enbrel was originally approved for rheumatoid arthritis in 1998, and many physicians are familiar with prescribing it. Patients give themselves injections of the drug under the skin, usually twice per week.

How is it different?
Enbrel is one of many "biologic response modifiers" that have been in development and testing for psoriasis and psoriatic arthritis. This new class of drugs is genetically engineered to block key interactions between cells in the immune system involved in these diseases. Other treatments for psoriasis and psoriatic arthritis, particularly those used in moderate to severe cases, can have a widespread impact on the immune system.

Enbrel blocks the action of a cytokine (cellular "messenger") called tumor necrosis factor-alpha (TNF-alpha) by binding to the site that allows the cell to communicate with other cells. Normally, TNF-alpha plays an important role in our immune system by promoting inflammation to fight infections. For unknown reasons, TNF-alpha is overproduced in the synovial fluid (lubricating fluid of the joints) and tissue of joints as well as the skin of people with psoriatic arthritis and psoriasis.

Thus, TNF-alpha overstimulates inflammation, which leads to painful damage of the joints and connective tissue, as well the development of lesions on the skin.

H w effectiv is Enbr l?
Enbrel is a maintenance drug. Once it is stopped, the symptoms of the disease return. Some patients will begin to experience improvement even after the first

injection. Many patients begin to experience improvements in the signs and symptoms of psoriatic arthritis after three to four weeks. By three months, a majority of patients in clinical trials experienced major improvement in both bone and skin disease.

In the last phase III trial before the drug was submitted to the FDA, 62 percent of patients on low doses of methotrexate who also took Enbrel achieved at least a 20 percent improvement in symptoms of psoriatic arthritis (tender and swollen joints, stiffness, pain, etc.) after three months.

Among patients who took Enbrel without methotrexate, 58 percent had at least a 20 percent improvement in their psoriatic arthritis. All patients received 25 milligrams of the drug twice a week and were compared to an equal number of patient who received no Enbrel.

Enbrel also appears to help improve the skin. After six months, 43 percent of patients with moderate to severe psoriasis achieved a 50 percent improvement in a typical lesion, and a 47 percent improvement in their psoriasis overall.

The trial included 205 patients at 17 clinics across the country.

What are the side effects?
In clinical trials, the principal side effects related to Enbrel were minor reactions at the site of injection (36 percent of patients). The injection site reactions have been reported to be like mosquito bites that tend to fade by themselves and are no reason to stop the medication.

Because Enbrel blocks the action of a cell (TNF-alpha) that normally plays an important role in the immune system, it is believed to affect a person's ability to fight infections. Physicians are encouraged to exercise caution when considering the use of Enbrel in patients with a history of recurring infections. However, in clinical trials, infectious events such as upper respiratory and urinary infections occurred with equal frequency between those taking Enbrel and those not, which is reassuring regarding the issue of predisposition to infection.

Recently, the FDA recommended that doctors test patients for tuberculosis (TB) before they take a drug similar to Enbrel called Remicade. Remicade is also an anti-TNF inhibitor, and it appears to contribute to the emergence of TB in patients who have a silent, or dormant, infection with TB. The same recommendation has not been made for Enbrel, but some rheumatologists nonetheless test any patient for dormant TB prior to prescribing anti-TNF therapy.

People with known multiple sclerosis should not take Enbrel. Since the drug was approved for rheumatoid arthritis, a handful of new or exacerbated multiple sclerosis cases has been seen. Physicians should advise their patients about this issue, but the risk is very small and in the great majority of patients outweighed by the potential benefits of the drug.

Based on all of the safety information available on Enbrel since the drug has been approved for rheumatoid arthritis, the FDA requires the warning label on the medication to state that the there is a risk of serious, even life-threatening, infections in some people, especially if their immune system is already compromised. The drug may be temporarily discontinued in people who have active infections, such as lung infections or flu.

Unlike the situation with methotrexate patients, regular blood tests to determine whether Enbrel is harming the liver will not be required.

How do I get it?

Immunex is requiring patients to join an enrollment program to receive Enbrel, but has not stated how long patients must wait before receiving the drug. According to company spokesperson Robin Shapiro, part of the reason the program is in place is to help the company monitor demand for the drug.

Patients who call the enrollment program (1-888-4-ENBREL) are asked for their names, address and mailing information. The company sends a package of information, including a release form patients are required to get their physician to sign. Before patients are placed on the waiting list, they need to send the signed form back to the company, as well as documentation that their insurance company will cover the drug.

According to Immunex, approximately 3,000 people per month are being moved from the waiting list to the active list to begin receiving Enbrel. Company officials say they do not know how many people are now on the waiting list, but that since 1998, Enbrel has been prescribed to 120,000 people.

Depending on where the drug is purchased, Enbrel costs approximately $12,000 per year.

Currently, Medicare does not cover prescription drugs, and so Enbrel is not covered. However, Immunex does report it has had great success working with people to get their private insurance companies to cover the treatment.

By calling the enrollment program number, patients can also talk to insurance specialists who can help walk them through the insurance process. The same number also puts patients in touch with nurses and allows them to order free needle disposal containers and sign up for prescription reminders, e-mail alerts and newsletters about Enbrel. The line is staffed Monday through Friday, from 9 a.m. to 9 p.m. EST.

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Cytokines

Cytokine
Protein secreted by a cell that signals other cells in a paracrine fashion or even itself (autocrine). The various lymphokines, chemokines, interferons, colony-stimulating factors, and tumor necrosis factors are examples. [cytokine receptors] Cytokines, unlike hormones, go to nearby cells, or even the cell that produced the signaling molecule, and work there. They usually do not pass into the blood. Hormones are created in special organs and pass into the blood to act at distant sites.

The term cytokine, or immunocytokines , was used initially to separate a group of immunomodulatory proteins, called also**immunotransmitters** , from other**Growth factors** that modulate the proliferation and bioactivities of non-immune cells. However, this terminology suggesting aclear-cut distinction cannot be maintained and may not be meaningful altogether. Some cytokines are produced by a rather limited number of different cell types while others are produced by almost the entire spectrum of known cell types.

The initial concept of "one producer cell -one cytokine -one target cell" has been falsified for almost every cytokine investigated more closely. A definition of these factors on the basis of their producer or target cells is therefore also problematic.

The same applies to classifications based upon identical or shared biological activities of cytokines especially with broad definitions (see, for example: BCDF (B-cell differentiation factors), BCGF (B-cell growth factors), Motogenic cytokines , Chemotactic cytokines (see: Chemokines), CSF (colony stimulating factors), angiogenesis factors, or TRF (T-cell replacing factors)) (for some personal views on aspects of nomenclature see also: Some personal remarks).

Designations such as HBGF (heparin-binding growth factors) take into account some biochemical shared by a variety of cytokines but are also problematic.

Today the term cytokine is used as a generic name for a diverse group of soluble proteins and peptides which act as humoral regulators at nano- to picomolar concentrations and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment (for some mechanistic concepts underlying cytokine actions see also: autocrine , paracrine , juxtacrine , retrocrine). Many growth factors and cytokines act as cellular survival factors by preventing programmed cell death (see: Apoptosis).

In many respects the biological activities of cytokines

resemble those of classical hormones produced in specialized glandular tissues. Some cytokines also behave like classical hormones in that they act at a systemic level, affecting, for example, biological phenomena such as inflammation , systemic inflammatory response syndrome , and acute phase reaction , wound healing , and the neuroimmune network .

In general, cytokines act on a wider spectrum of target cells than hormones. Perhaps the major feature distinguishing cytokines from mediators regarded generally as hormones is the fact that, unlike hormones, cytokines are not produced by specialized cells which are organized in specialized glands, i. e. there is not a single organ source for these mediators. The fact that cytokines are secreted proteins also means that the sites of their expression does not necessarily predict the sites at which they exert their biological function.

Some cytokines have been found, upon determination of their primary structures, to be identical with classical enzymes (see, for example: ADF (adult T-cell leukemia-derived factor), nm23 , PD-ECGF (platelet-derived endothelial cell growth factor), neuroleukin). Cytokines normally do not possess enzymatic activities although there is a growing list of exceptions.

The biological activities of cytokines can be measured by a variety of Bioassays employing, among other

things, Factor-dependent cell lines , or by other assays using, for example, antibodies (see also: Cytokine assays , WHO cytokine standardization). RT-PCR quantitation of cytokines employs modern techniques of molecular biology and detects the presence of mRNA encoding specific cytokines.

In the more restricted sense cytokines comprise Interleukins , initially thought to be produced exclusively by leukocytes, Lymphokines , initially thought to be produced exclusively by lymphocytes, Monokines , initially thought to be produced exclusively by monocytes, interferons (see: IFN), initially thought to be involved in antiviral responses, colony stimulating factors (see: CSF), initially thought to support the growth of cells in semi-solid media (see also: Colony formation assay), Chemokines , thought to be involved in Chemotaxis , and a variety of other proteins.

The term**Type-1 cytokines** refers to cytokines produced by Th1 T-helper cells while**Type-2 cytokines** are those produced by Th2 T-helper cells. Type-1 cytokines include IL2 , IFN-gamma , IL12 and TNF-beta , while Type-2 cytokines include IL4 , IL5 , IL6 , IL10 , and IL13 .

It has been suggested that the generic term**Peptide regulatory factors** (abbrev. PRF) be used for all these factors to avoid the general difficulties with the nomenclature (see also: Some personal remarks). This term has the advantage that it includes also a

number of low molecular mass peptides which are generally not regarded as cytokines although they have many activities of cytokines. Some of these low molecular weight proteins and peptides have been referred to as**Minicytokines** .

Most cytokines are unrelated in terms of sequence although some can be grouped into families (see: Gene family ; see also: Cytokine receptor families) or are classified into categories according to the types of secondary and tertiary structure.

IFN-alpha , IFN-beta , IFN-omega , IL2 , IL3 , IL4 , IL5 , IL6 , IL7 , IL9 , G-CSF , M-CSF , GM-CSF , and PDGF , for example, have an alpha-spiral secondary structure. Beta-structural cytokines include IL1-alpha , IL1-beta , TNF-alpha , TNF-beta , and FGF . Composite structures (alpha +beta) are observed, among other things, with IL8 , IFN-gamma , IP-10 , PF4 , GRO , 9E3 . According to the type of tertiary structure, alpha-spiral proteins can be grouped further into IFN like and IL2 like families, and beta-structural proteins can be grouped into IL1 like and TNF like families. For other aspects of biochemistry see also: Recombinant cytokines , Muteins , Peptide mimetics .

Most cytokines are glycoproteins which are secreted by cells using classical secretory pathways (see also: signal sequence). Many genes encoding cytokines can give rise to a variety of variant forms of cytokines by means of alternative splicing, yielding

molecules with slightly different but biologically significant bioactivities. In many cases the expression patterns of different forms of cytokines or of members of a cytokine family are overlapping only partially, suggesting a specific role for each factor.

Membrane-bound forms have been described also for many cytokines, and some may be associated also with the extracellular matrix . It is likely that the switching between soluble and membrane forms of cytokines is an important regulatory event (see also: Autocrine , paracrine , juxtacrine , retrocrine). In some cases membrane forms of a cytokine have been found to be indispensable for normal development, with soluble forms being unable to entirely substitute for them.

Most cytokines are generally not stored inside cells (exceptions are, for example TGF-beta and PDGF which are stored in platelets). The expression of most cytokines is regulated tightly at practically all levels: these factors are usually produced only by cells after cell activation in response to an induction signal. Expression can be regulated at the level of transcription, translation, and protein synthesis (see also: gene expression ; ARE (AU-rich element)). is Normally, cytokines are expressed transiently only but constitutive expression has been observed also. The expression of many cytokines also seems to be regulated differentially, depending on cell type and developmental age. Secretion or release from producer cells is a regulated process. Once released,

their behaviour in the circulation may be regulated by soluble receptors and specific or unspecific binding proteins. Regulation also is at work at the receptor level on target cells and at the level of signaling pathways governing alterations in the behaviour of responder cells.

Most cytokines were detected initially in functional tests in vitro as biochemically undefined activities or as distinct factors with distinct biological activities. This also explains, at least in part, the plethora of different names for some of the cytokines. In many instances these activities were named after a particular biological activity observed in an in vitro assay (see also: Bioassays and Cytokine assays for alternatives) or after cells that were found to elaborate these factors (for techniques allowing identification of cytokine genes, cytokine receptor genes, and other relevant genes without prior knowledge of their activities see: Gene library). One should be aware of the fact that at this moment in time the relevance of many in vitro activities of cytokines to their endogenous functions within an intact organism is not clearly defined.

Almost all cytokines are pleiotropic effectors showing multiple biological activities. In addition, multiple cytokines often have overlapping activities and a single cell frequently interacts with multiple cytokines with seemingly identical responses (cross-talk). One of the consequences of this functional overlap is the observation that one factor may frequently

functionally replace another factor altogether or at least partially compensate for the lack of another factor. Since most cytokines have ubiquitous biological activities, their physiologic significance as normal regulators of physiology is often difficult to assess.

Studies of gene functions in experimental transgenic animals in which a cytokine gene has been functionally inactivated by gene targeting (see also: Knock-out) are of particular importance in research on cytokines because, unlike in vitro studies, they provide information about the true in vivo functions of a given cytokine by highlighting the effects of their absence. In many instances these studies have shown that null mutations of particular cytokine genes do not have the effects in vivo expected from their activities in vitro. If information about loss-of-function studies is available for a given cytokine or its receptor and if I had time to add the information it can be found as a special subentry (Transgenic/Knock-out/Antisense studies) for each particular cytokine.

Many cytokines show stimulating or inhibitory activities and may synergise or antagonize also the actions of other factors. A single cytokine may elicit reactions also under certain circumstances which are the reverse of those shown under other circumstances. The type, the duration, and also the extent of cellular activities induced by a particular cytokine can be influenced considerably by the

micro-environment of a cell, depending, for example, on the growth state of the cells (sparse or confluent), the type of neighboring cells, cytokine concentrations, the combination of other cytokines present at the same time, and even on the temporal sequence of several cytokines acting on the same cell. Under such circumstances combinatorial effects thus allow a single cytokine to transmit diverse signals to different subsets of cells.

The fact that every cell type may have different responses to the same growth factor can be explained, at least in part, by different spectrums of genes expressed in these cells and the availability and levels of various transcription factors that drive Gene expression . The responses elicited by cytokines are therefore contextual and the "informational content", i. e. the intrinsic activities of a given cytokine may vary with conditions. Although a variety of cytokines are known to share at least some biological effects the observations that single cells usually show different patterns of gene expression in response to different cytokines can be taken as evidence for the existence of cytokine receptor-specific signal transduction pathways. Shared and different transcriptional activators that transduce a signal from a cytokine receptor to a transcription regulatory element of DNA are involved in these processes (for some examples see: STAT proteins , Janus kinases , IRS).

It has been observed, for example, that bFGF is a

strong mitogen for fibroblasts at low concentrations and a chemoattractant at high concentrations (see also: Chemotaxis). bFGF has been shown also to be a biphasic regulator of human hepatoblastoma-derived HepG2 cells, depending upon concentration. The interferon IFN-gamma can stimulate the proliferation of B-cells prestimulated with Anti-IgM, and inhibits the activities of the same cells induced by IL4 . On the other hand, IL4 activates B-cells and promotes their proliferation while inhibiting the effects induced by IL2 in the same cells. The activity of at least two cytokines (IL1-alpha and IL1-beta) is regulated by an endogenous receptor antagonist, the IL1 receptor antagonist (see: IL1ra). Several cytokines, including TNF , IFN-gamma , IL2 and IL4 , are inhibited by soluble receptors (see also: Receptor shedding , Cytokine inhibitors , retrocrine). Several cytokines, including IL10 and TGF-beta , act to inhibit other cytokines.

The processes responsible for the regulation of cytokines are not well understood. Cells utilize distinct biochemical pathways converging on mediator release and these can be probed, among other things, by employing a variety of substances mimicking or inhibiting the actions of cytokines (see, for example: Bryostatins , Calcium ionophore , Genistein , H8 , Herbimycin A , K-252a , Lavendustin A , Phorbol esters , Okadaic acid , Staurosporine , Suramin , Tyrphostins , Vanadate).

Frequently one observes a hierarchical order of

cytokine actions with some early Cytokines preactivating cells so that they then can respond to late-acting cytokines (see also: Cell activation). Many cytokines induce the synthesis of novel gene products once they have bound to their respective receptors (see: ERG , Early response gene). Some of the novel products are themselves cytokines (see: Chemokines , for example). In addition, there are a variety of biological response modifiers that function as Anti-cytokines .

Cytokine mediators can be transported quickly to remote areas of a multicellular organism. They can address multiple target cells and can be degraded quickly. Concentration gradients can be used to elicit specific responses. These possibilities by far exceed the possibilities provided by mere cell-to-cell contacts within a multicellular organism. It can be assumed that cytokines play a pivotal role in all sorts of cell-to-cell communication processes although many of the mechanisms of their actions have not yet been elucidated in full detail.

A close examination of the physiological and pathological effects of the regulated or deregulated (see: Transgenic animals) expression of cytokines in complex organisms has shown that these mediators are involved in virtually all general systemic reactions of an organism (see also: CytokineTopics), including such important processes as the regulation of immune responses (see, for example: BCDF , B-cell growth and differentiation factors; BCGF , B-cell

growth factors ; TRF , T-cell replacing factors ; Isotype switching), inflammatory processes (see: Inflammation), hematopoiesis (see also: Hematopoietins), and wound healing .

Cytokines are important mediators involved in embryogenesis and organ development (see also: Angiogenesis) and their activities in these processes may differ from those observed postnatally. In addition they play a key role in neuroimmunological, neuroendocrinological, and neuroregulatory processes (see: Neuroimmune network). Cytokines are important positive or negative regulators of mitosis (see also: Cell cycle), differentiation, migration (see also: Chemotaxis , Chemokines), cell survival and cell death (see also: Apoptosis), and transformation (see also: Oncogene). It has been shown that a number of viral infectious agents exploit the cytokine repertoire of organisms to evade immune responses of the host. Virus-encoded factors (see also: Virulence Factors MiniCOPE Dictionary .) appear to affect the activities of cytokines in at least four different ways: by inhibiting the synthesis and release of cytokines from infected cells; by interfering with the interaction between cytokines and their receptors; by inhibiting signal transmission pathways of cytokines; and by synthesizing virus-encoded cytokines that antagonize the effects of host cytokines mediating antiviral processes (see: Viroceptor , Virokine). Bacteria and other micro-organisms also appear to produce cytokine-like

substances which they utilize to subvert host responses (see: Bacteriokine , Microkine).

Cytokines themselves rarely are related closely among each other in terms of primary sequences. Some appear to have some common three-dimensional features and some of them can be grouped into families. For example, the TNF ligand superfamily members (with the exception of LT-alpha) are type II membrane glycoproteins with homology to TNF in the extracellular domain (overall homologies, 20 percent. The HBNF family includes members of the group of fibroblast growth factors . Another group of diverse factors with conserved sequence features are the Chemokines . The analysis of crystal structures of several cytokines with very little sequence homology has revealed a common overall topology that is not deducible from sequence comparisons (see: Cystine knot growth factor family).

The biological activities of cytokines are mediated by specific membrane receptors which can be expressed on virtually all cell types known. Their expression is also subject to several regulatory mechanisms (see: Receptor transmodulation) although some receptors are expressed also constitutively.

Cytokine receptor proteins have been shown to share a number of characteristics. Many receptors are members of cytokine receptor families . Many receptors are multi-subunit structures that bind

ligands and at the same time possess functions as signal transducers due to their intrinsic tyrosine kinase activity (see also: Autophosphorylation ; see also: PTK ; protein tyrosine kinase). Many receptors often share common signal transducing receptor components in the same family (see also: Cytokine receptor families), which explains, at least in part, the functional redundancy of cytokines. It is the cross-communication between different signaling systems that eventually allows the integration of a great diversity of stimuli, which a cell can be subjected to under varying physiological situations. This and the ubiquitous cellular distribution of certain cytokine receptors has hampered attempts to define critical responsive cell populations and the physiologically important cell-specific functions of cytokines in vivo. Many receptors are associated with special signal transducing proteins in the interior of the cell (see, for example Janus kinases , STAT proteins). Some receptors may bind more than one cytokine. Several cytokine receptors have been shown to be converted into soluble binding proteins that regulate ligand access to the cell by specific proteolytic cleavage of receptor ectodomains.

The many specific activities of individual cytokines have been the basis for current concepts of therapeutical intervention, in particular of the treatment of hematopoietic malfunctions and tumor therapy. Applications involve the support of chemo- and radiotherapy, bone marrow transplantation, and

general immunostimulation (see also: Adoptive immunotherapy , LAK cells , TIL , Cytokine gene transfer , Cytokine fusion toxins).

Although some recombinant cytokines are now in clinical use, and and attempts are made to develop hybrid molecules from known cytokines (see: Muteins) which possess the advantages of the respective factors, but not their disadvantages, one must be aware of the fact that current knowledge is still limited. Cytokines are powerful two-edged weapons that can trigger a cascade of reactions, and may show activities that often go beyond the single highly specific property which it is hoped they possess. New factors are being discovered constantly and they extend our knowledge about the Cytokine network .

Nevertheless it can be stated that our new (and growing) understanding of the biological mechanisms governing cytokine actions are an important contribution to medical knowledge. The biochemistry and molecular biology of cytokine actions explain some well-known and sometimes also some of the more obscure clinical aspects of diseases. Knowledge that cytokines create regulatory hierarchies and provide independent and/or interrelated regulatory mechanisms that can confer distinct and interactive developmental functions lays a solid, albeit rather complicated foundation, for current and future clinical experiences.

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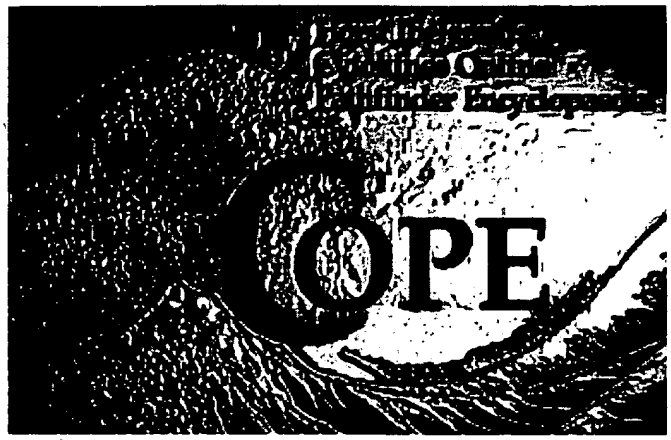

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Chemokines

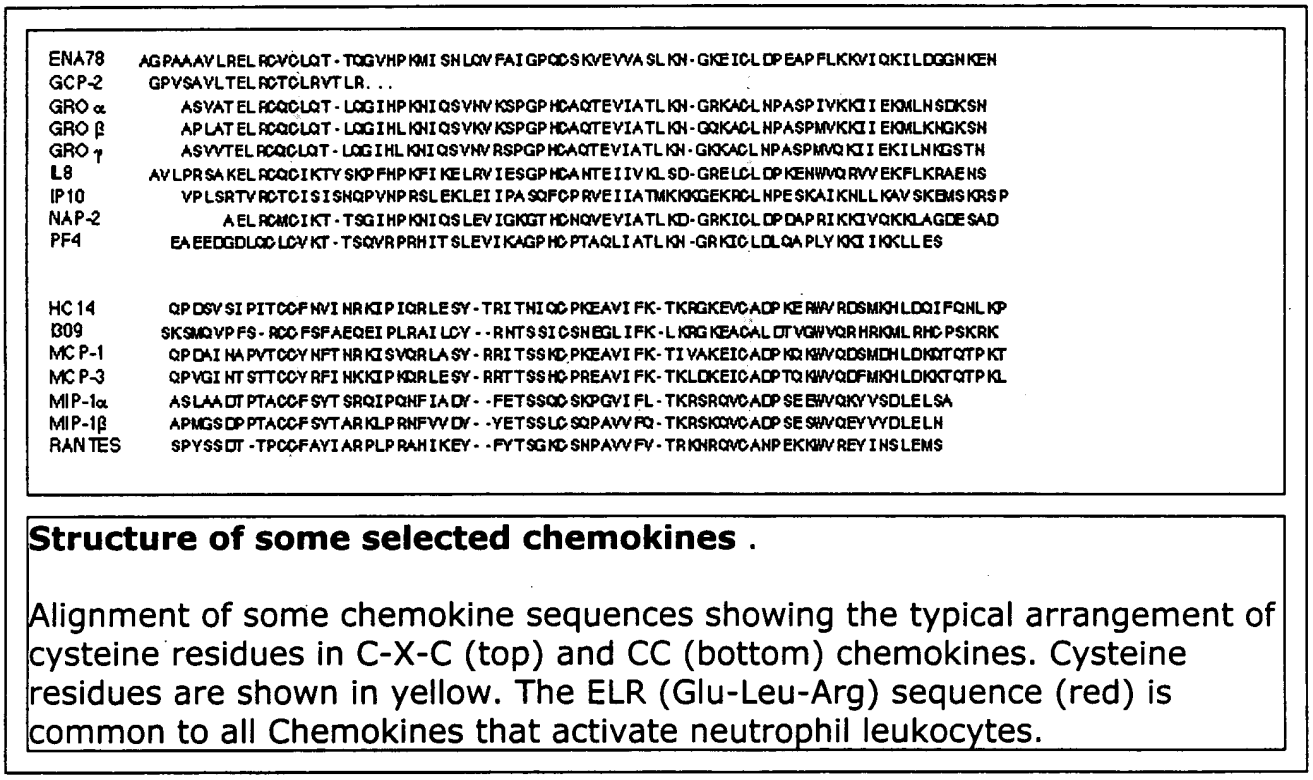
New generic name given to a family of pro-inflammatory activation-inducible cytokines (see also: Cell activation) previously referred to as members of**SIS family of cytokines** ,**SIG family of cytokines** ,**SCY family of cytokines** ,**Platelet factor-4 superfamily** or**Intercrines** (see also: Gene family). These proteins are mainly chemotactic for different cell types (hence the name, which is derived from (chemo)tactic cyto(kines); see also: Chemotaxis).

Chemokines have molecular masses of 8-10 kDa and show approximately 20-50 percent sequence homology among each other at the protein level. The proteins also share common gene structures and tertiary structures. All Chemokines possess a number of conserved cysteine residues involved in intramolecular disulfide bond formation.

According to the chromosomal locations of individual genes two different subfamilies of chemokines are distinguished. Members of the**Alpha-Chemokines** are referred to also as the**4q chemokine family** because the genes encoding members of this family map to human chromosome 4q12-21. The first two cysteine residues of members of this family are separated by a single amino acids and these proteins, therefore, are called also**CXC-Chemokines** . For a new sytematic nomenclature of this group see also SCY family of cytokines . Some members of the subgroup of the human CXC-Chemokines are defined by the conserved**ELR sequence motif** (glutamic acid-

leucine-arginine) immediately preceding the first cysteine residue near the amino-terminal end. Chemokines with an ELR sequence motif have been found to chemoattract and activate primarily neutrophils. Chemokines without the ELR sequence motif appear to chemoattract and activate monocytes, dendritic cells, T-cells, NK-cells, B-lymphocytes, basophils, and eosinophils.

Members of the**Beta-Chemokines** or**17q chemokine family** map to human chromosome 17q11-32 (murine chromosome11). The first two cysteine residues are adjacent and, therefore, these proteins are called also**CC-Chemokines** (for a new sytematic nomenclature of this group see also SCY family of cytokines). Some of the Beta-Chemokines contain two additional conserved cysteine residues and sometimes the term**C6-beta-Chemokines** is used for this subgroup.



Structure of some selected chemokines .

Alignment of some chemokine sequences showing the typical arrangement of cysteine residues in C-X-C (top) and CC (bottom) chemokines. Cysteine residues are shown in yellow. The ELR (Glu-Leu-Arg) sequence (red) is common to all Chemokines that activate neutrophil leukocytes.

The**C-Chemokines** or**Gamma-Chemokines** differ from the other chemokines by the absence of a cysteine residue. Members of the small group of chemokines with a**CXXXC cysteine signature motif** are referred to as**Delta-Chemokines** or**CX3C-Chemokines** or**CXXXC-Chemokines**). These proteins are type-1 transmembrane glycoproteins with the chemokine domain resting on top of an extended mucin-like stalk. A soluble form of the chemokine moiety can be released from its transmembrane anchor by extracellular cleavage.

The existence of clearly defined subgroups of chemokines on the basis of structural and functional properties illustrates the importance of

chemoattractant diversity in the regulation of leukocyte movement through the body.

Overview: the members of the four major classes of chemokines				
	C	CC	CXC	CX3C
		6Ckine 464.1 744.1	3-10C 9E3	
A	ATAC	ABCD-1 ABCD-2 ACT-2 ALP AMAC-1	AMCF-1 AMCF-2 AIF ANAP Angie Angie-2	ABCD-3
B			beta-R1 Beta-Thromboglobulin BCA-1 BLC blr-1 ligand BMAC bolekine BRAK	
C		C10 CCF18 CCK1 CCL1 CCL2 CCL3 CCL4 CCL5 CCL6 CCL7 CCL8 CCL9 CCL10 CCL11 CCL12 CCL13 CCL14 CCL15 CCL16 CCL17	C7 cCAF CEF-4 CINC CINC-2-alpha CINC-2-beta CINC-2-beta-like CKA-3 CRG-2 CRG-10 CTAP-3 CXCL1 CXCL2 CXCL3 CXCL4 CXCL5 CXCL6 CXCL7 CXCL8 CXCL9 CXCL10	

		CCL18 CCL19 CCL20 CCL21 CCL22 CCL23 CCL24 CCL25 CCL26 CCL27 CCL28 Ck-beta-1 Ck-beta-4 Ck-beta-6 Ck-beta-7 Ck-beta-8 Ck-beta-8-1 Ck-beta-9 Ck-beta-10 Ck-beta-11 Ck-beta-12 Ck-beta-15 CTACK	CXCL11 CXCL12 CXCL13 CXCL14 CXCL15 CXCL16	
D		DC/B-Ck DC-CK1	DNA binding protein	
E		ELC Eotaxin Eotaxin-2 eotaxin-3 ESkine Exodus-1 Exodus-2 Exodus-2	ECIP-1 EDNAP ENA-78 ENAP ENAP-alpha ENAP-beta Endothelial cell growth inhibitor Endothelial IL8	
F		FIC	FDNCF FINAP	Fractalkine
G		G26 GDCF GDCF-2 GOS-19-1 GOS-19-2 GOS-19-3	GCF GCP-2 GRO1 GRO2 GRO3 GRO-alpha GRO-beta GRO-gamma	

H		H400 HC-11 HC-14 HC-21 HCC-1 HCC-2 HCC-3 HCC-4	H174 Heparin neutralizing protein Humig	
I		I-309 ILC ILINCK IMAC	I-TAC Ifi10 IL8 IP-9 IP-10 IRH	
J		JE	JSC	
K		K203	KC K60 KEC KS1	
L	Lymphotactin	L2G25B LAG-1 LARC LCC-1 LD78-alpha LD78-beta LD78-gamma LDCF LEC Lkn-1 LMC	LAI LCF LA-PF4 LDGF LDNAP LIF LIX LUCT Lungkine LYNAP	
M		Manchester inhibitor MARC MCAF MCIF MCP-1 MCP-2 MCP-3 MCP-4 MCP-5 MDC MEC MIP-1-alpha MIP-1-beta	M119 MDGF MDNAP MDNCF Megakaryocyte-stimulatory-factor MGSA MGSA-alpha MGSA-beta Mig MIP-2 MIP-2-alpha MIP-2-beta MIP-2-gamma	

		MIP-1-delta MIP-1-gamma MIP-3 MIP-3-alpha MIP-3-beta MIP-4 MIP-4-alpha MIP-5 Monotactin-1 MPIF-1 MPIF-2 MRP-1 MRP-2 Mtn-1	mob-1 MOC MONAP	
N		NC28 NCC-1 NCC-2 NCC-3 NCC-4	N51 NAF NAP-1 NAP-2 NAP-3 NAP-4 NAP S NCF NCP NJAC	Neurotactin
O			Oncostatin A	
P		P16 P500 PARC pAT464 pAT744 PESKY	PBP PBP-like PBSF PF4 PF4-ALT PF4-ALT PF4V1 PLF PPBP	
R		RANTES Regakine-1		
S	SCM-1-alpha SCYC1 SCYC2	SCI SCYA1 SCYA2 SCYA3 SCYA4 SCYA5 SCYA6 SCYA7	SCYB1 SCYB2 SCYB3 SCYB4 SCYB5 SCYB6 SCYB7 SCYB8	SCYD1 SR-PSOX

		SCYA8 SCYA9 SCYA10 SCYA11 SCYA12 SCYA13 SCYA14 SCYA15 SCYA16 SCYA17 SCYA19 SCYA20 SCYA21 SCYA22 SCYA23 SCYA24 SCYA25 SCYA26 SCYA27 SCYA28 SIS-alpha SIS-beta SIS-delta SIS-epsilon SIS-gamma skinkine SLC SMC-CF ST38 STCP-1	SCYB9 SCYB9B SCYB10 SCYB11 SCYB12 SCYB13 SCYB14 SCYB15 SCYB16 SDF-1-alpha SDF-1-beta SR-PSOX	
T		TARC TCA-3 TCA-4 TDCF TECK TSC-1 TSG-8 TY5	TCF TCK-1 TLSF-alpha TLSF-beta TPAR-1 TSG-1	trout chemokine 2
W			WECHE	

This alphabetical list of chemokines groups them into their respective families. Many of these factors have been described under different names and thus appear several times

The biological activities of chemokines are mediated by specific receptors and

also by receptors with overlapping ligand specificities that bind several of these proteins which always belong either to the CC-Chemokines or the group of CXC-Chemokines. Lymphocytes require stimulation to become responsive to most known chemokines, and this process is linked closely to chemokine receptor expression. Chemokine receptors belong to the large group of G-protein-coupled seven transmembrane domain receptors which contain seven hydrophobic alpha-helical segments that transverse the membrane. These receptors form a structurally related group within the superfamily of G-protein-coupled receptors which mediate signaling via heterotrimeric G-proteins.

The receptors that bind CXC-Chemokines are designated**CXCR** followed by a number (see: **CXCR1**, **CXCR2**, **CXCR3**, **CXCR4**, **CXCR5**) while those binding CC-Chemokines are designated**CCR** followed by a number (see: **CCR1**, **CCR2**, **CCR3**, **CCR4**, **CCR5**, **CCR6**, **CCR7**, **CCR8**, **CCR9**, **CCR10**). For viral chemokine receptor homologs see also: ECRF-3, EBI-1 (EBV-induced gene-1), US28. For viral inhibitors of chemokine activities see also: vCCI, vCKBP. All chemokines have been shown to be capable of binding to heparin moieties of the extracellular matrix. Binding to heparan sulfate or heparin has been shown to enhance neutrophil responses to IL8.

Chemokines are essential mediators of normal leukocyte trafficking but their role is not restricted to cell attraction. Chemokines are multipotent cytokines that localize and enhance Inflammation by inducing chemotaxis and cell activation of different types of inflammatory cells typically present at inflammatory sites (see also: Motogenic cytokines). Chemokines and other mediators are secreted also by these cells. Most factors are induced and released into the circulation during acute infection but high concentrations of some chemokines are observed also in normal plasma.

Chemokines have been shown to exert their effects on distinct subsets of cells. CXC-Chemokines, for example appear to attract neutrophils but not macrophages, while CC-Chemokines preferentially induce migration of macrophages. Some chemokines have been shown to induce selective migration of leukocyte subsets.

It is now assumed that the combinatorial effects of multiple chemokines and other mediators are responsible for the cellular composition at inflammatory sites. In addition, many chemokines also directly cause cell activation. Some of them activate granulocytes and/or monocytes and cause respiratory bursts, degranulation, and the release of lysosomal enzymes. Others prime immune cells to respond to sub-optimal amounts of other inflammatory mediators (see also: Inflammation). Yet others have been shown to be potent histamine releasing factors for basophils. It has been proposed that erythrocytes through their promiscuous chemokine receptor play an important role in regulating the chemokine network. Chemokines bound to the erythrocyte receptor are known to be inaccessible to their normal target cells. This appears to provide a sink for superfluous chemokines and may serve to limit the systemic effects of these

mediators without disrupting localized processes taking place at the site of Inflammation .

Many genes encoding chemokines are expressed strongly during the course of a number of pathophysiological processes including autoimmune diseases, cancer, atherosclerosis, and chronic inflammatory diseases.

Certain CC-Chemokines exhibit biological activities other than mere chemotaxis . Some chemokines have been shown to be capable of inducing the proliferation and activation of killer cells known as CHAK (CC-Chemokine-activated killer), which are similar to cells activated by IL2 (see: LAK cells).

Some chemokines may have important developmental functions also apart from inducing Chemotaxis (see, for example: SDF). Several chemokines have been shown to modulate the growth of hematopoietic progenitor cell types and may thus have functions in hematopoiesis also (see, for example: BFU-E , CFU-GM , CFU-GEMM) and may play a role in trafficking of hematopoietic progenitor cells in and out of the bone marrow in inflammatory conditions. A number of additional functions of chemokines on angiogenesis , wound healing , tumor growth, metastasis, development, and genesis, homeostasis and function of the immune system have been reported also.

The importance of chemokines is underlined by the observation that chemokines and their receptors are especially important in the control of viral infection and replication. Some chemokines interfere with viral propagation by enhancing the cytotoxic activity of infected cells or by recruiting activated leukocytes to foci of infection to aid viral clearance. A medically important discovery is the observation that chemokines can suppress infection by HIV-1 and that chemokine receptors serve, along with CD4 , as obligate coreceptors for HIV-1 entry. Many viruses encode viral homologs of chemokines or chemokine binding proteins, termed virokine and viroceptor , respectively (see also: Virulence Factors MiniCOPE Dictionary).

For a strategy allowing manipulation of the cell surface expression of chemokine receptors that are involved in the pathogenesis of HIV virus infections (CCR5 and CXCR4) and thus also allowing a modification of cell susceptibility see also: intrakine .

date of last revision: March 2002

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Centocor Places Congestive Heart Failure Clinical Program On Hold

Malvern, PA (October 22, 2001) - Centocor, Inc., announced today that, following evaluation of the preliminary results of an ongoing Phase II clinical trial, further development of REMICADE® (infliximab) for the treatment of patients with advanced congestive heart failure (CHF) has been placed on hold. The results demonstrated no improvement in patients' clinical status and showed higher incidence of mortality and hospitalization for worsening heart failure in patients treated with REMICADE®, especially those treated at the higher dose of 10 mg/kg.

This trial evaluated three infusions of REMICADE® 5 mg/kg, REMICADE® 10 mg/kg, or placebo over six weeks in patients with NYHA Class III-IV congestive heart failure. These patients typically experience either a marked limitation in, or a complete inability to, carry on any form of physical activity.

Over the next several weeks, Centocor will continue to follow patients who participated in the trial to better characterize the risks posed to patients with advanced CHF. In the interim, Centocor, in consultation with the U.S. Food and Drug Administration (FDA), has mailed a "Dear Doctor" letter communicating these preliminary results to health ca professionals nationwide, and providing guidance on the management of pa receiving REMICADE® who have concomitant CHF. (A copy of this letter ca at www.remicade.com.)

Although experimental preclinical studies and previous small clinical trials s that therapy targeted at tumor necrosis factor (TNF) might be of benefit in with CHF, this and other recent trials have failed to demonstrate that agen TNF can improve the clinical course in these patients.

"Centocor is committed to ensuring that REMICADE® is used safely and eff said Jerry Boscia, M.D., vice president of clinical research and development more than 170,000 patients treated worldwide since its introduction in 199 benefit-to-risk ratio of REMICADE® is well established." He added that the fully committed to continuing its clinical development program for REMICAI other indications.

REMICADE® was the first biologic approved by the FDA for short-term use with Crohn's disease who have had inadequate response to conventional th

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REMICADE® is also indicated, in combination with methotrexate, for reduc signs and symptoms and inhibiting progression of joint damage in patients moderately to severely active rheumatoid arthritis who have had an inadec response to methotrexate alone.

Centocor is a leading biopharmaceutical company that creates, acquires an cost-effective therapies that yield long-term benefits for patients and the h community. Its products, developed primarily through monoclonal antibod technology, help physicians deliver innovative treatments to improve huma and restore patients' quality of life. Centocor is a wholly owned subsidiary Johnson, a worldwide leader in health care products. For more information REMICADE® labeling, visit Centocor's Web site at www.centocor.com.

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